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New galenic process for omeprazole containing pellets.

A production method for pellets containing Omeprazole performed with an inert matrix based on sodium starch and glucose, said core covered with the micronized and sieved active substance which is in a buffered suspension being added with an anionic surface active agent, in order to finally receive an enteric coating in a fluidized bed with HPMC levoglucosan, diethyl phthalate, acetone and ethyl alcohol being afterwards dried to obtain a water content of less than 1% weight and encapsulated.

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A new production method for enteric coated pellets containing Omeprazole which is coated on an inert core in the form of pH buffered dispersion phase.

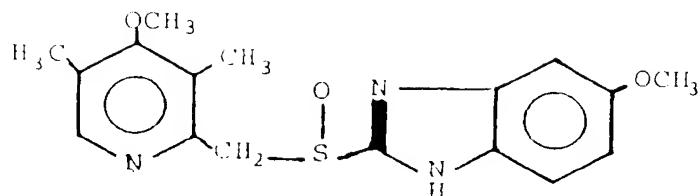
Field of invention:

The present invention is related to a new production method of a stable preparation containing Omeprazole for oral administration.

Description of invention:

Omeprazole is a potent inhibitor of gastric acid secretion. Omeprazole is a pyridine benzimidazole derivative with the following total formula $C_{17}H_{17}N_3O_2S$ and a molecular weight of 354.4.

Structure formula:



Omeprazole (1) is readily degradable in acidic environments, pH less than 7. Stability profile of 1 is almost the same in solid phase, and is also affected by moisture and organic solvents. The reason why oral dosage forms of Omeprazole have to be formulated as enteric coated dosage form is to protect it from acidic gastric juice (Ref US Patent 4 786 505 Nov 22, 1988). Enteric coated pellets of Omeprazole should reasonably withstand the gastric juice but it must be dissolved rapidly in the small intestine to obtain acceptable bioavailability of course the effect. Several coating methods and materials have been used to comply the above mentioned prerequisites of Omeprazole (UK Patent GB 21 89 698).

In this patent application a new process for the preparation of orally used hard gelatin capsules containing enteric coated Omeprazole pellets is described.

This new enteric coated pellet production process consists of the following four steps

- I Preparation of inert core by conventional pan coating method
- II Active coating by using rotary type fluidized bed
- III Protective coating by using rotary type fluidized bed
- IV Enteric coating by using rotary type fluidized bed

I. The contents of inert core are as following

Sucrose 65-85%

Corn Starch 15-25%

Glucose 2-6%

Particle size distribution range is arranged to be 90% within 0.71 mm to 0.85 mm (in diameter) by suitable sieving. These inert pellets can also be obtained commercially.

II To obtain a rapid dispersion active (Omeprazole) substance is micronized and sieved through 150 mesh sieves

The active substance sieved is dispersed in a buffered aqueous dispersion, at pH 7.1 ± 0.1, of a macromolecular binding agent. A anionic surface active agent (Sodium Lauryl Sulphate) is added to the aqueous phase to increase the wettability and smooth dispersion of Omeprazole.

The aqueous dispersion is sprayed on to the inert pellets in the cabin of a rotary type fluidized bed machine under appropriate process parameters.

The content of active dispersion phase for one dose (one capsule) is as following

Omeprazole 20 mg.

Hydroxypropyl methyl cellulose 5.3 mg.

Lactose anhydrous 8 mg.

L-Hydroxy propyl cellulose **6 mg.**
Sodium lauryl sulphate **0.5mg.**
Disodium hydrogen phosphate dihydrate **0.8 mg.**
Water **0.21 ml.**

III Active coated pellets have to be protected from the organic solvent which is normally used to disperse the enteric coating material.

The thickness of this layer is experimentally determined to obtain an optimal protection during the enteral coating processes and the necessary amount of coating material per capsule (one dose) for above mentioned active coated pellets (> 100 passes through 15 mesh sieves) has been determined as following:

HPMC **3.4 mg.**

Water **0.06 ml.**

Aqueous molecular dispersion of HPMC is sprayed under appropriate process parameters onto the active coated pellets in the cabinet of a rotary type fluidized bed machine and dried until the water content of the pellets is less than 1% when determined by the toluen distillation method described in USP XXII.

IV Enteric coating is performed in the same machine using appropriate process parameters by spraying the following coating solution:

HPMC phthalate **24 mg.**

Diethyl phthalate **0.13 mg.**

Aceton **225 mg. (... ml)**

Ethyl alcohol **96 mg. (... ml)**

Finished product is sieved through 15 mesh and 20 mesh sieves. Pellets which pass through 15 mesh and are retained on 20 mesh sieves, are filled to gelatin capsules. Capsule contents are $233 \text{ mg} \pm 10\%$.

II. Protective Coating phase

Machine: Gatt GPCG 60 with GRG 30

Active coated pellets: **25 kg ± 0.4**

Spray nozzle: **2 x 1.8 mm**

Nozzle position: **Tangential**

Filter type: **PB** (2% of cotton wod)

Sieve type: **Rotor Disc**.

Inlet air Temperature: **50-60 °C**

Inlet Air Rate: **700-800 m³/h**

Pumping rate: **20 rpm**

Sieve width: **2 mm**

Rotor Speed: **300 rpm**

III Enteric coating Phase

Machine: Gatt GPCG 60 with GRG 30

Spray nozzle: **2 x 1.8 mm**

Nozzle position: **Tangential**

Filter type: **PB2**

Sieve type: **Rotor Disc**

Air inlet angle: **40-50°**

Flow speed: **1000 rpm**

Claims

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capsule, characterized in that the process is performed to obtain an inert core covered with the micronized active substance, to be easily enteric coated and dried after the adjusting of its granulometry, being in this way ready to be prepared as capsules.

5. 2. A production method of pellets containing Omeprazole according to the previous claim, characterized in that the inert nucleous includes a 65-85% of sacarose, 15-25% of starch and 2-36% of glucose, said nucleous being obtained by conventional means and being sieved through a mesh within 0.71 and 0.85 mm.
10. 3. A production method according to the first claim, characterized in that the active substance is micronized and sieved through a 150 mesh to be dispersed in a buffered aqueous dispersion at pH 7.1 ± 1% with the addition of an anionic surface active agent, as for example sodium lauryl sulphate.
15. 4. A production method according to the first claim, characterized in that the active substance comprising Omeprazole, hydroxil methyl cellulose, lactose anhydrous, L-hydroxy propyl-celluloso, sodium lauryl sulphate, disodium hydrogen phosphate dihydrate and water is sprayed onto the inert pellets in the cabin of a rotary type fluidized bed machine.
20. 5. A production method according to the first claim, characterized in that the entire cover is produced in a fluidized bed with HPMC phthalato, diethyl phthalato, aceton and ethyl alcohol being afterwards dried to obtain a water content of less than 1%.

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EUROPEAN SEARCH REPORT

Application Number

EP 91 50 0066

DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document with indication, where appropriate, of relevant passages | Relevant to claim | CLASSIFICATION OF THE APPLICATION (Int. Cl.5) |
|----------|---|-------------------|---|
| Y,D | GB-A-2 189 698 (AKTIEBOLAGET HASSEL) * page 1, line 6 - line 8 * * page 2, line 25 - page 3, line 37 * * page 5 - page 6; example 2 * * page 6 - page 7; example 5 * --- | 1,3-5 | A61K9/54 A61K31/44 |
| Y | DE-A-3 901 151 (HOECHST A.G.) * page 13; example 11 * --- | 1,3-5 | |
| A | FP-A-0 256 933 (ETHYPHARM) * page 2, line 61 - page 3, line 4 * | 2 | |
| A | EP-A-0 237 506 (LEJUS MEDICAL AKTIEBOLAG) * page 2, line 37 - line 43 * * page 3, line 13 - line 15 * * page 4; example 1 * | 1-5 | |
| | ----- | | |

TECHNICAL FIELDS SEARCHED (Int. Cl.5)

A61K

The present search report has been drawn up for all claims.

Place of search

Date of completion of the search

Examiner

particularly relevant if taken alone
particularly relevant if combined with another
document of the same category
A technological background
(O) non-written disclosure
(P) intermediate document

earlier patent document, but published
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A member of the same patent family, corresponding
document

